

suspension medium of the preparations, usually water, by a factor of at least 10 and in that the content of solubilizing components is less than 0.1 mole percent, based on the content of these substances, at which the solubilization point of the enveloped droplets is reached or this solubilization point cannot be reached] comprising transfersomes suspended in a pharmaceutically acceptable medium for application onto the skin or mucous membrane of a mammal, said transfersomes comprising liquid droplets encompassed within a sheath comprising at least two amphiphilic lipid components which differ in their solubility in said pharmaceutically acceptable medium by a factor of at least 10, said two amphiphilic compounds being selected such that said transfersomes are capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized.

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3. (Amended) The preparation of claim [claims] 1 [and 2], wherein the solubility [characterized in that the solubility, especially the water solubility] of the more soluble component(s) [is/are] is at least  $10^{-3}$  to  $10^{-6}$  M and the solubility[, especially the water solubility,] of the less soluble component(s) is[/are] at least  $10^{-6}$  to  $10^{-10}$  M.
  4. (Amended) The preparation of [one of the claims] claim 1 [to 3], wherein [characterized in that] the difference between the solubility of the more soluble component(s) and the less soluble component(s) is approximately between 10 and  $10^7$  [,preferably between  $10^2$  and  $10^6$  and especially between  $10^3$  and  $10^5$ ].
  5. (Amended) The preparation of [one of the claims] claim 1, [to 4] wherein [characterized in that the ability of ] the preparation [to permeates] through said skin or mucous membrane [constrictions is] at least 0.001% [and preferably 0.1%] of the permeability of small molecules, which permeate essentially without being impeded.
  6. (Amended) The preparation of [one of the claims] claim 1 [to 5], wherein [characterized in that the ratio of] the permeation capability relative to reference particles  $P_{(transfer.)}/P_{(refer.)}$ ,

the reference particles being [, for example] water [, much smaller than the constrictions in the barrier, when the barrier itself is the site of the determination,] is between  $10^{-5}$  and 1[, preferably between  $10^{-4}$  and 1 and especially between  $10^{-3}$  and 1].

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7. (Amended) The preparation of [one of the claims] claim 1 [to 6], wherein said transfersomes contain an active agent in said liquid droplet, in said sheath, or in both said liquid droplet and said sheath [characterized in that the preparations contain at least two amphiphilic components of different solubility, for forming a carrier substance and/or a membrane-like sheath about a droplet amount of hydrophilic liquid, wherein the active ingredient is contained in the carrier substance in or at the membrane-like sheath and/ or in the hydrophilic liquid].
  8. (Amended) The preparation of [one of the claims ] claim 1 [to 7], wherein [characterized in that] the vesicle radius of the [enveloped droplets] transfersome is between about 25 nm and about 500 nm [, preferably between about 50 and about 200 nm and especially between 80 and about 100 nm].
  9. (Amended) The preparation of [one of the claims]1 to 8, characterized in that] claim 7, wherein the sheath is a double layer.
  10. (Amended) The preparation of [[one of the claims] claim 1 [to 9, characterized in that] , wherein said [the] amphiphilic components [component (n) comprises or] comprise [physiologically tolerated] lipids of different polarity [and/ or such an active ingredient or ingredients].
  11. (Amended) The preparation of [one of the claims] 1 [to 10], wherein [characterized in that the] at least one amphiphilic [substance comprises a] lipid component [or lipoid of biological origin or a corresponding synthetic lipid or a derivative of such lipids, particularly] is selected from the group consisting of a diacyl or a dialkyl

glycerophosphoethanolamino azo polyoxyethylene derivative, a didecanoyl phosphatidyl choline, a diacyl phosphooligomaltobionamide, a glyceride, a glycerophospholipid, a isoprenoid lipid, a sphingolipid, a steroid, a sterol, a sulfur-containing or a hydrocarbon-containing lipid or a different lipid, which forms stable structures, such as double layers, [preferably comprises] a half protonated liquid fatty acid, [particularly] a phosphatidyl choline, a phosphatidyl ethanolamine, a phosphatidyl glycerol, a phosphatidyl inositol, a phosphatid acid, a phosphatidyl serine, a sphingomylein or a sphingophospholipid, glycosphingolipid [(such as], a cerebroside, a ceramide polyhexoside, a sulfatide, a sphingoplasmalogen[],] a ganglioside or other glycolipid, or a synthetic lipid, [preferably] a dioleoyl, a dilinoloyl, a dilinolenyl, a dilinoloyl, a dilinolinoyl or a diarachinoyl, a dilauroyl, a dimyristoyl, a dilalmitoyl, a distearoyl phospholipid or a corresponding dialkyl or a sphingosin derivative, a glycolipid or other identical chain or a mixed chain acyl lipid [or] and an alkyl lipid.

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12. (Amended) The preparation of [one of the claims ] claim 1 [to 11] wherein [characterized in that] the less soluble amphiphilic lipid component is selected from the group consisting of [comprises a synthetic lipid, preferably] a myristoleoyl, a palmitoleoyl, a petroselinyll, a petroselaidyl, a oleoyl, elaidyl, a cis- or trans- vaccenoyl, a linolyl, a linolenyl, a linolaidyl, a octadecatetraenoyl, a gondooyl, a eicosoenoyl, a eicosadienoyl, a eicosatrienoyl, a arachidoyl, a cis- or trans-docosaeenoyl, a docosadienoyl, a docosatrienoyl, a docosatetraenoyl, a caproyl, a lauroyl, a tridecanoyl, a myristoyl, a pentadecanoyl, a palmitoyl, a heptadecanoyl, a stearoyl or a nonadecanoyl, a glycerophospholipid or a corresponding chain-branched derivative or a corresponding sphingosin derivative, a glycolipid or an [different] acyl lipid or a alkyl lipid; and the more soluble component or components [is] derived from one of the less soluble components [listed above and, for increasing the solubility, is] derivatized with a butanoyl, a pentanoyl, a hexanoyl, a heptanoyl, a octanoyl, a nonanoyl, a decanoyl, a dodecane, [or] a undecanoyl, [or] a [corresponding] monosaturated substituent thereof, [or] a polyunsaturated substituent thereof [or] and a chain-branched substituent thereof, [or]

several substituents, selected independently of one another, and/or is substituted, complexed and/or associated with a different material, which is suitable for improving the solubility].

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13. (Amended) The preparation of [one of the claims] claim 1 [to 12], wherein [characterized in that] the total content of the amphiphilic components [substance for administration on human or animal skin] is between 0.01 and 40 % by weight of the preparation [, preferably between 0.1 and 15% by weight and especially between 1 and 10% by weight].

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15. (Amended) The preparation of [one of the claims] claim 1 [to 14], wherein [characterized in that, as] the active ingredient [, it contains] is selected from the group consisting of an adrenocorticostatic agent, a β-adrenolytic agent, an androgen or antiandrogen, an anti-parasitic, an anabolic, an anesthetic or an analgesic, an analeptic, an anti-allergic, an anti-arrhythmic, an anti-arteriosclerosis, an anti-asthmatic [and/]or a bronchospasmolytic agent, an antibiotic, an anti-depressive [and/]or an anti-psychotic agent, an anti-diabetic agent, an antidote, an anti-emetic, an anti-epileptic, an anti-fibrinolytic, an anti-convulsive or an anti-cholinergic agent, an enzyme, a coenzyme, [or] a corresponding coenzyme inhibitor, an antihistamine, an antihypertensive drug, a biological activity inhibitor, an antihypotensive agent, an anticoagulant, an anti-mycotic, [or] an antimyasthenic agent, an active ingredient against Parkinson's or Alzheimer's disease, an anti-phlogistic, a anti-pyretic or an anti-rheumatic agent, an antiseptic, a respiratory analeptic or a stimulating agent, a broncholytic, a cardiotonic or a chemotherapeutic agent, a coronary dilator, a cytostatic agent, a diuretic, a ganglion blocker, a glucocorticoid, a therapeutic agent for influenza, a hemostatic agent, a [or] hypotonic agent, an immunoglobulin or a fragment or a different immunological or a receptor substance, a bioactive carbohydrate, a bioactive carbohydrate [(J)derivative]], a contraceptive, a migraine agent, a mineral corticoid, a morphine antagonist, a muscle relaxant, a narcotic, a neural therapeutic agent or a CNS therapeutic agent, a nucleotide or a polynucleotide, a neuroleptic agent, a neuron transmitter, [or] a [corresponding

antagonist] neuron transmitter antagonist, a peptide, a peptide [or derivative[ ]], an ophthalmic agent, a [(para)]-sympathicomimetic or [(para)]-sympathicolytic agent, a protein, a protein [(derivative[ ])], a psoriasis/neurodermatitis agent, a mydriatic agent, a mood elevator, a rhinological agent, a sleeping draft or [its] a sleeping draft antagonist, a sedative, a spasmolytic, a tuberculosis agent or a urological agent, a vasoconstrictor or a vasodilator, a virostatic agent or a wound-healing agent, [or several such agents, especially] diclofenac [or] and ibuprofen.

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16. (Amended) The preparation of [one of the claims] claim 1 [to 15], wherein [characterized in that] the active ingredient is a nonsteroidal anti-inflammatory drug[, for example,] selected from the group consisting of diclofenac, ibuprofen, [or a] and a lithium, sodium, potassium, cesium, rubidium, ammonium, monoethyl, dimethyl, trimethylammonium or ethylammonium salt thereof.
  17. (Amended) The preparation of claim 10 [one of the claims1 to 16], wherein [characterized in that] the less polar amphiphilic lipid component is a phospholipid. [comprises a physiologically compatible lipid, preferably from the class of phospholipids and especially from the class of phosphatidylcholines,] and a second, more soluble amphiphilic component is an [and the] active ingredient [is the more soluble component, optionally with the addition of less than 10% by weight, based on the total composition of the preparation, of a further soluble component, which is the more soluble component,] the concentration of the more soluble component(s) [typically] being between 0.01% by weight and 15% by weight [, preferably between 0.1% by weight and 10% by weight and particularly between 0.5% by weight and 3% by weight, and the total lipid concentration being between 0.005% by weight and 40% by weight and preferably between 0.5% by weight and 15% by weight and especially between 1% by weight and 10% by weight].
  18. (Amended) The preparation of [one of the claims] claim 1 [to 17], wherein [characterized in that] the preparation comprises consistency modifiers[, such as] selected from the

group consisting of a hydrogel[s], an antioxidant[s] selected from the group consisting of [such as] a probucol, a tocopherol, a BHT, an ascorbic acid, a desferroxamine [and /]or a stabilizer[s such as] selected from the group consisting of a phenol, a cresol, and a benzyl alcohol [, etc].

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22. (Amended) The preparation of [one of the claims] 1 [to 18], wherein [characterized in that] the active ingredient is a growth regulating substance [for living beings].
20. (Amended) The preparation of [one of the] claim[s] 1 [to 18], wherein [characterized in that] the active ingredient [has biocidal properties and, in particular, is] is selected from the group consisting of an insecticide, a pesticide, a herbicide or a fungicide.
21. (Amended) The preparation of [one of the claims] claim 1 [to 18], wherein [characterized in that] the active ingredient is an allurement [in particular a pheromone].
- (Amended) A method for producing a preparation for transporting [the administration, application or transport of] at least one active ingredient through [, particularly for medicinal or biological purposes, into and through natural barriers and constrictions, such as] the skin or mucous membrane of a mammal, [and the like,] comprising: [in the form of]
- a. selecting at least two amphiphilic lipid components which differ in their solubility in a pharmaceutically acceptable medium by a factor of at least 10;
  - b. suspending transfersomes containing said at least two amphiphilic lipid components in said pharmaceutically acceptable medium for application onto the skin or mucous membrane, said transfersomes comprising liquid droplets encompassed within a sheath comprising said at least two amphiphilic lipid components, said amphiphilic lipid components being selected such that said transfersomes are capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized [liquid droplets, which can be suspended in a liquid medium and are provided

with a membrane-like sheath of one or a few layers of amphiphilic carrier substance, the carrier substance comprising at least two physiochemically different components, characterized in that]

c. including one or more solubilizing components to provide adequate deformability to said transfersomes to pass through said skin or mucous membrane without being solubilized, if necessary, such that [at least two amphiphilic components are selected, which differ in their solubility in the suspension medium of the preparation, usually water, by a factor of at least 10 and] the content of solubilizing components is less than 0.1 mole percent, based on the content of said amphiphilic lipid components, at which the solubilizing point of the enveloped droplets is reached; and

d. adjusting the content of amphiphilic lipid components such that [based on the content of these substances, at which, the solubilizing point of the enveloped droplets is reached or this point cannot be reached in a practically relevant region, and the content of the amphiphilic components is adjusted, so that] the ability of the transfersomes [preparation] to permeate through [constrictions is at least] said skin or mucous membrane is from about 0.001% to about 0.1% of the permeability of [small molecules, for example, of] water.

23. (Amended) The method of claim 22, wherein [characterized in that] the content of said amphiphilic components [is] are adjusted, so that [the ratio of] the permeation [capability] relative to water [reference particles, which are much smaller than the constrictions in the barrier, for example water, when the barrier itself is the site of determination,] is between  $10^{-5}$  and 1 [,preferably between  $10^{-4}$  and 1 and especially between  $10^{-2}$  and 1].

24. (Amended) The method of [claims] claim 22 [and 23, characterized in that] wherein [stability and] the permeation capability [are] is determined by filtration, [optionally] under pressure, through a fine-pored filter or [through otherwise] by controlled

mechanical whirling up, shearing or comminuting.

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25. (Amended) The method of [one of the claims] claim 22 [to 24, characterized in that],  
wherein [the substance mixture for producing a transfersome-like preparation is subjected to] said transfersomes are produced by a method selected from the group consisting of [a] filtration, [to a] treatment with ultrasound, [to] stirring, [to] shaking [or to] and other mechanical comminuting effects.
  26. (Amended) The method of [one of the claims] claim 22 [to 25, characterized in that]  
wherein the transfersome[-like droplets, which form the preparation, are] preparation is produced from at least two amphiphilic components of different polarity, at least one polar liquid and at least one active ingredient.
  27. (Amended) The method of claim [one of the claims] 22, [to 26, characterized in that]  
wherein [the transfersome-like droplets, which form the preparation, wherein the] said amphiphilic component(s) comprises or contains the active ingredient, and said transfersomes are formed from at least two amphiphilic components of different polarity and at least one polar liquid.
  28. (Amended) The method of [one of the claims] claim 22 [to 28, characterized in that the]  
wherein said amphiphilic components and [the] a hydrophilic substance [in each case] are mixed separately with [the] an active ingredient and optionally brought into solution, [the mixtures or solutions are] and then combined to form transfersomes [into a mixture, in which droplet formation is brought about by supplying, in particular, mechanical energy].
  29. (Amended) The method of [one of the claims] claim 22 [to 28, characterized in that the]  
wherein said amphiphilic components, either as such or dissolved in a physiologically compatible solvent or a dissolving intermediary, which is miscible with a polar liquid or liquids, [especially with water,] are combined with a polar solution.

30. (Amended) The method of claim [one of the claims] 22 [to 29, characterized in that], wherein [the formation of enveloped droplets] said transfersomes are formed by a method selected from the group consisting of [is brought about by] stirring; [, by] evaporation from a reverse phase; [, by] an injection method; [or] a dialysis method; [, by] electrical stressing; [,] thermal stressing; [ or] a mechanical stressing [, such as] selected from the group consisting of shaking, stirring, homogenizing, ultrasonication, rubbing, freezing, [or] thawing, heating, [or] and cooling; [, or] high pressure filtration; and [or] low pressure filtration.

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31. (Amended) The method of [one of the claims] claim 22 [to 30, characterized in that], wherein the formation of the [enveloped droplets] transfersomes is brought about by filtration and the filter material used in said filtration has a pore size of 0.01  $\mu\text{m}$  to 0.8  $\mu\text{m}$  [, especially of 0.05 to 0.3  $\mu\text{m}$  and particularly of 0.08 to 0.15  $\mu\text{m}$ , several filters optionally being connected in series].

32. (Amended) The method of [one of the claims] claim 22 [to 31, characterized in that] further comprising including an active ingredient in said transfersomes, and forming said transfersomes such that the association between [carrier and active ingredients] said transfersomes and said active ingredient takes place at least partially after transfersome [the droplet] formation.

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33. (Amended) The method of [one of the claims] claim 22 [to 32, characterized in that] wherein shortly before use, the [enveloped droplets] are prepared from a concentrate or lyophilisate.

Please add the following new claims:

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--34. (New) The preparation of claim 4, wherein the difference between the solubility of the more soluble component(s) and the less soluble component(s) is approximately between

$10^2$  and  $10^6$ .--

- 35. (New) The preparation of claim 4, wherein the difference between the solubility of the more soluble component(s) and the less soluble component(s) is approximately between  $10^3$  and  $10^5$ .--
- 36. (New) The preparation of claim 6, wherein the permeation capability relative to reference particles  $P_{(transfer.)}/P_{(refer.)}$ , the reference particles being water is between  $10^{-4}$  and 1.--
- 37. (New) The preparation of claim 6, wherein the permeation capability relative to reference particles  $P_{(transfer.)}/P_{(refer.)}$ , the reference particles being water is between  $10^{-2}$  and 1.--
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--38. (New) The preparation of claim 8, wherein the vesicle radius is between about 50 nm and about 200 nm.--
- 39. (New) The preparation of claim 8, wherein the vecicle radius is between about 80 nm and about 100 nm.--
- 40. (New) The preparation of claim 13, wherein the total content of the amphiphilic components is between about 0.1 and 15% by weight.--
- 41. (New) The preparation of claim 13, wherein the total content of the amphiphilic components is between about 1 and 10% by weight.--
- 42. (New) The preparation of claim 17, wherein the concentration of the more soluble component(s) is between 0.1% by weight and 10% by weight.--
- 43. (New) The preparation of claim 17, wherein the concentration of the more soluble component(s) is between about 0.5% by weight and 3% by weight.--

- 44. (New) The preparation of claim 17, wherein the total lipid concentration being between about 0.5% by weight and 15% by weight.--
- 45. (New) The preparation of claim 17, wherein the total lipid concentration being between about 1% by weight and 10% by weight.--
- 46. (New) The preparation of claim 1, further comprising one or more solubilizing components in an amount effective to provide adequate deformability to said transfersomes, such that said transfersomes are capable of passing through said skin or mucous membrane without being solubilized, the amount of solubilizing components included in said preparation being less than 0.1 mole percent at which the solubilizing point of the enveloped droplets is reached, based on the content of said amphiphilic lipid components. --
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- 47. (New) The preparation of claim 1, further comprising an active ingredient contained in said sheath. --
- 48. (New) The preparation of claim 1, further comprising an active ingredient contained in said liquid droplets. --
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- 49. (New) The method of claim 23, wherein the permeation relative to reference particles, is between  $10^{-4}$  and 1.--
- 50. (New) The method of claim 23, wherein the permeation relative to reference particles, is between  $10^{-2}$  and 1.--
- 51. (New) The method of claim 31, wherein the filter material has a pore size of 0.05 to 0.3  $\mu\text{m}$ .--